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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,135	09/08/2000	Kazuko Hirabayashi	44342.011800	2368

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,135	HIRABAYASHI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 4 and 8 are pending.

Applicant's traversal, the cancellation of claims 5 and 11 and the amendment to claim 4 filed on 1/9/06 is acknowledged and considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Desmyter et al. (Texas Reports on Biology and Medicine 35:516-522, 1977) taken with Yano et al., (YANO 1, US Patent No. 5,298,614, cited on a prior PTO-892) and Bever et al. (Journal of Interferon Research, 5: 423-428, 1985) and Liaw (J. Gastroenterol. Hepatol. 1997, 12:S346-53) in further view of Yano (YANO 2, EP 06854557A1, IDS).

Desmyter teaches that interferon and interferon inducers (e.g., Poly IC) have been studied for treating hepatitis in a patient and chimpanzees (page 516). Desmyter teaches that Poly IC complexes with poly-L-lysine and carboxymethylcellulose were administered to chimpanzees that have a chronic hepatitis B infection (page 518). Two courses with the complexes were given to the chimps: 3mg/kg daily for one week and every other day for another week and, six month later, 3 mg/kg daily for 2 weeks and every other day for a total of 7 weeks (page 518). Both courses resulted in treatment of the hepatitis B infection (pages 518-519). Desmyter teaches that the administration of Poly IC to the mammals results in direct action of interferon in the liver (page 519). However, Desmyter does not specifically teach intravenously, hepatic intra-arterially, or transmucosally administering a complex comprising administering a cationic liposome with 1μg to 50 mg/man of poly IC, which has a mean length within the range of 100 to 500bp.

However, at the time the invention was made, YANO 1 teaches that poly I: poly C is a substance having interferon induction action and can be used for treating viral infections (abstract and column 3, lines 32-40). YANO 1 further teaches that the substance can be used as

a pharmaceutical substance in humans (column 16). YANO 1 further teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity (column 4, lines 31-39). YANO 1 teaches that the fact that the control of molecular size of nucleic acid polymer within a specified range is the primarily important factor for remarkable reduction of toxicity of poly I: poly C and the preferred molecular size for using poly I: poly C is from 100 to 600 base numbers (column 11, lines 13-34). YANO 1 further teaches that the dsRNA can be delivered to an individual using different routes of delivery, including subcutaneous, intramuscular, or intravenous (column 18, line 32-46).

In addition, at the time invention was made, Bever teaches i.v. administration of 100 μg/kg Poly IC in humans, wherein the administration of Poly IC produced substantial levels of IFN (pages 86-89). Bever teaches that substantial levels of IFN were produced when Poly IC was administered weekly, biweekly and monthly (page 86). In addition, in view of the levels of IFN produced by administering Poly IC to a human taught by the prior art (e.g., Desmyter and Bever), one of ordinary skill in the art would have reasonably expected that Poly IC could be used to treat hepatitis in a human with a reasonable expectation of success.

In addition, at the invention was made, Liaw teaches that interferon (IFN) is widely used for treating HBV, HCV, and HDV (page S346).

However, Desmyter, YANO 1, Bever, and Liaw do not specifically teach using the complex (2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid, e.g., lecithin) in the method.

However, at the time the invention was made, YANO 2 teaches using a complex (2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid, e.g., lecithin) to administer double stranded RNA to an individual and that using the lipid reduces toxicity of the double stranded RNA and improves the uptake efficiency of the double stranded RNA into cells ('457, abstract and pages 2-11). YANO 2 teaches that the complex can be delivered intravenously, intrarterially, locally, and rectally (page 16).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever, Liaw, and YANO 2 to treat hepatitis C in a human using intravenous or transmucosal administration of a complex comprising a cationic liposome with 1 μg to 50 mg/man of poly IC which has a mean length within the range of 100 to 500 bp; once, every day, every other day, weekly, or bi-weekly and inducing interferon chiefly in the liver in a human. One of ordinary skill in the art would have been motivated to use the complex for treating hepatitis C in a human because Poly IC was well known to one of ordinary skill in the art for inducing interferon in a patient for treating hepatitis.

In addition, one of ordinary skill in the art would have been motivated to use 3mg to 100 μg/man of Poly IC for treating hepatitis C in a human because the prior art teaches one of ordinary skill in the art that these concentrations of Poly IC would produce a sufficient amount of interferon *in vivo* to treat hepatitis in a human and one of ordinary skill in the art would make the necessary modifications to the concentration of Poly IC to practice the claimed method. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Furthermore, one of ordinary skill in the art would have been motivated to use intravenous or transmucosal administration to deliver the complex to treat hepatitis C in a human

because the prior art teaches one of ordinary skill in the art that both routes of administration produce enough IFN to treat hepatitis in a human.

Furthermore, one of ordinary skill in the art would have been motivated, as a matter of designer choice, to deliver the complex once, every day, every other day, weekly, bi-weekly to treat hepatitis in a human because the prior art teaches one ordinary skill in the art that these regimens would produce enough IFN to treat hepatitis in a human.

Furthermore, one of ordinary skill in the art would have been motivated to use Poly IC which has a mean length within the range of 100 to 500bp of Poly IC as taught by YANO 1 for treating hepatitis in a human because this range displays reduced toxicity of the double stranded RNA in vivo.

In addition, at the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever and Liaw in further view of YANO 2 to use 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid (e.g., lecithin) with poly I:C in the method. One of ordinary skill in the art would have been motivated to use 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid (e.g., lecithin) with poly I:C for treating hepatitis C in a human because the lipid reduces toxicity of the double stranded RNA in vivo and improves the uptake efficiency of the double stranded RNA into cells of the individual.

In addition, at the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever, and Liaw in further view of YANO 2 to use i.v., hepatic intra-arterial, or transmucosal administration of the complex to treat hepatitis C in a human. One of ordinary skill in the art would have been

motivated to use the administration routes to deliver the complex to treat hepatitis in a human because the prior art teaches one of ordinary skill in the art that these routes of administration would produce enough IFN to treat hepatitis C in a human and these administration routes were well known to one of ordinary skill in the art for delivering Poly IC to a mammal. In addition, one of ordinary skill in the art would have been motivated to use hepatic intra-arterial administration because hepatitis results in the inflammation of the liver and one of ordinary skill in the art would determine that the liver would be the target area for inducing interferon using Poly IC.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/9/06 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. In view of the large amount of knowledge of using Poly IC to treat hepatitis provided in the prior art, one of ordinary skill in the art would make the necessary modifications to practice the claimed method. See the references used in the 103 rejection and Tytell et al. (Proc. Soc. Exp. Biol. Med. 135 :917-21, 1970). With respect to the limitation directed to the dosage of Poly I: Poly C used in the claimed method. MPEP 2144.05 recites:

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

This is the case here. The specification (page 8) does not disclose that the limitations in instant claims 4 and 8 are critical for one of ordinary skill in the art to practice the claimed invention. Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use 1 μg to 50 mg/man per dose of Poly I: PolyC which has a mean length within the range of 100 to 500 bp once through three times a day, every day, every other day, or on a weekly or fortnightly basis in the method. One of ordinary skill in the art would have been motivated to use either range because the range taught by the Desmyter et al. taken with YANO 1 and Bever et al. and Liaw in further view of YANO 2 is an obvious variant of the limitations in instant claims 4 and 8 and one of ordinary skill in the art would make the necessary modifications to the dosage to practice the claimed method.

In response to applicant's argument that in view of the teaching of YANO1, it would not have been obvious to use unmodified Poly IC compared to modified Poly IC because unmodified Poly IC has an activity weaker than that of Poly IC derivatives, the argument is not found persuasive because a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S.

975 (1989). As stated above, the large amount of knowledge of using Poly IC to treat hepatitis provided in the prior art, one of ordinary skill in the art would make the necessary modifications to practice the claimed method.

In response to applicant's argument that far from being weak, 500-600 bp short chained poly IC can not induce IFN by itself, the response to not found persuasive because YANO1 teaches using Poly IC which has mean length within the range of 100 to 600 bp to induce interferon with reduce toxicity. Also See Tytell et al. (supra). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). There is no evidence of record to support applicant's argument. In addition, it appears that applicants are admitting on page 6 of applicant's argument that using 500-600 bp short-chained Poly IC in the claimed method is not considered enabled. Clarification is requested.

In response to applicant's argument that the complex of the present invention is entirely different from that of interferon itself, poly IC alone, or poly IC in pharmacological action or effect, the argument is not found persuasive because the poly IC recited in the claimed method is same material that is taught by the prior art. The claimed cationic liposome reduces toxicity of the double stranded RNA and improves the uptake efficiency of the double stranded RNA into cells as taught by YANO 2. The selection of a known material based on its suitability for its intended use supports a *prima facie* obviousness determination. See Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

In response to applicant's argument that in view of Table 3 (argument filed on 7/28/05), the chain length of 100-500bp according to the present invention is so short that the IFN

inducing activity of Poly IC of 100-500bp is expected to be very weak, the argument is not found persuasive because Table 3 is an in vitro example. The prior art teaches that the chain length of Poly IC effects interferon activity in vitro more than interferon activity in vivo. See Black et al. (Antimicrobial agents and chemotherapy, 3:198-206, 1973) and Tytell et al. (supra). Tytell teaches that "the maximal activity of Poly depended on an average molecule weight of $1.9x10^5$ (550 residues) or greater, while full activity of Poly C was still retained when the average molecule weight was reduced to as little as $2.3x10^4$ (70 residues). See pages 920-921.

In response to applicant's argument that it would not have been obvious if the present complex containing 100-500bp short-chained poly IC which did not possess IFN-inducing activity by itself, could induce enough IFN for the treatment of human hepatitis, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). There is no evidence of record to support applicant's argument.

Response to Arguments

Applicant's arguments, see page 3, filed 1/9/06, with respect to new matter rejection have been fully considered and are persuasive. The rejection of claims 4, 5, 8, and 11 has been withdrawn because of the amendment to claim 4 and the cancellation of claims 5 and 11.

Applicant's arguments, see pages 3 and 4, filed 1/9/06, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 4, 5,

8, and 11 has been withdrawn because of the amendment to claim 4 and the cancellation of claims 5 and 11.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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